CLINICAL PROGRESS
Symposium: Anticoagulants and Coronary Artery Disease

Introduction

By CARLETON B. CHAPMAN, M.D.

The anticoagulant story, as we know it in clinical medicine, may logically be said to have begun in Howell’s laboratory at Johns Hopkins when Jay McLean, a medical student, discovered heparin. The details of the development were traced in a historical symposium—edited by one of our speakers—which was published in 1959. But a few of the high spots may be of interest.

Jay McLean (1891-1957) went to Hopkins in 1915, having graduated from the University of California the year before. Dr. Howell put him to work on thromboplastic substances obtained from brain tissue but McLean, branching out on his own, soon turned to extracts from other organs. German workers had previously obtained what they called heparphosphatid from horse liver by extracting it with ether. Working with such an extract, McLean found that after further purification and after the cephalin in the extract had deteriorated, an anticoagulant agent was left.* It was Howell and Holt (1918) who coined the word heparin.†

Subsequent work, much of it in Best’s laboratory, had to do with production and purification of heparin. There were studies of its in vivo effect but not until 1938 did Solandt and Best try it in experimental coronary occlusion. A year later, they (with Nassim) made the highly significant statement: “Since over ten per cent of the deaths associated with coronary thrombosis in man are caused by embolic sequelae of mural thrombus formation, a clinical trial of heparin is indicated.” But the war intervened and the suggestion could not be implemented.

A little earlier, in February 1933 to be exact, farmer Ed Carlson brought about a hundred pounds of spoiled sweet clover to the Biochemistry Building of the University of Wisconsin. In the next 6 or 7 years, Link and his colleagues isolated Dicumarol (1941), an anticoagulant agent which was very promptly subjected to experimental scrutiny at Wisconsin and at several other centers. The whole story is told in amusing detail by Professor Link in the symposium edited by Dr. Wright.

Dr. Wright, in fact, comes into the narrative in 1938 via a severe attack of thrombophlebitis which he suffered after an operation. A little later, he was responsible for using heparin in the treatment of acute migrating thrombophlebitis and a few years later (1942) he published one of the early reports on the use of Dicumarol in human beings. In the same year he and his colleagues began to treat patients suffering from myocardial infarction with Dicumarol. The results of this experience were published.

* “The heparphosphatid . . ., when purified by many precipitations in alcohol at 60° has no thromboplastic action and in fact shows a marked power to inhibit the coagulation (1916).”
† In their words, describing one of two new factors: “. . . First, a phosphatid, not previously described, which exists in various tissues but is found in greatest abundance in the liver. This phosphatid is designated as heparin to indicate its origin from liver.”

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in 1946 and, in the same year, the famous cooperative study, with Dr. Wright as chairman, was authorized by the American Heart Association. Dr. Wright and colleagues published a progress report in 1948 and a full report 6 years later. Their conclusion, that “anticoagulant therapy should be used in all cases of coronary thrombosis with myocardial infarction unless a definite contraindication exists,” is widely accepted in this country and in some foreign ones. The conclusion has never been uncontested but the frequency of serious attacks on it has seemed to decrease in recent years. Recommendations that anticoagulants be used indefinitely to prevent myocardial infarction, or in the treatment of angina pectoris, have never been as widely accepted as the admonition that all patients with myocardial infarction should be so treated. But that particular view is now so prevalent in this country that it takes a brave man to stand up and question it publicly.

But in Denmark, it has recently been challenged definitely and vigorously. Dr. Tage Hilden and co-workers, beginning in 1955, began to amass data which they believe justify the conclusion that “... anticoagulant therapy is not indicated in acute myocardial infarction.” Their study is a large one and, although it has been the object of a number of attacks, it has had the effect of reopening the whole question concerning the routine use of anticoagulants in the treatment of acute myocardial infarction. It is indeed rather astonishing that objections to such a widely, and often enthusiastically, accepted therapeutic measure so stubbornly refuse to be put down. It would seem that the extremists are moderating a bit; there are few today who still claim that anticoagulants as used clinically are completely efficacious in preventing thrombosis and embolism; nor are there many who hold that anticoagulants are totally worthless. But in between these views many questions remain to be answered.

We are most fortunate in having the two men with us who are most likely to be able to resolve some of these questions and to indicate clearly the points of difference that remain to be settled.

References
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